REMARKS

In view of the foregoing amendments and the following representations, reconsideration and allowance of the above-identified application is respectfully requested.

Status of the Claims:

Claims 1-37, 40-42 and 46 have been cancelled without prejudice.

Claims 38, 39, 43-45 and 47-55 are currently pending in the application.

Claim 38, 51 and 52 have been amended to recite specific formulation components for the enteric coating of the first pellet and the sustained release coating of the second pellet. Support for the amendments to these claims can be found in the specification as originally filed at page 9, line 17 to page 10, line 14.

35 U.S.C. § 103(a):

On page 2 of the Office Action, the Examiner rejected claims 38-55 under 35 U.S.C. §103(a) as being unpatentable over the teachings of Midha et al., WO 00/59479 ("Midha") in view of Percel et al., United States Published Patent Application No. 2001/0046964 ("Percel").

Reconsideration and withdrawal of this rejection is respectfully requested.

The pending claims have been amended to recite a bupropion composition, tablet or capsule that is administered to a patient once a day to produce a specific *in vivo* plasma profile. The claimed composition, tablet or capsule comprises three separate and distinct bupropion components:

1) an immediate release component that releases the bupropion upon administration of the composition to a patient;

2) a first pellet consisting of a first core containing a pharmaceutically acceptable salt of bupropion and an enteric coating applied to the first core wherein the enteric coating consists of:

(i) a pH dependent coating polymer selected from the group consisting of shellac, methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate,

hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate and mixtures thereof; (ii) a plasticizer; and (iii) a lubricant; and wherein the first pellet releases bupropion in the upper gastrointestinal tract of a human patient [at a pH of about 4.8 (claims 53-55)]; and 3) a second pellet comprising a second core containing a pharmaceutically acceptable salt of bupropion and a sustained release coating applied to the second core wherein the sustained release coating comprises a mixture of (i) a water insoluble polymer; (ii) a methyl acrylic acid copolymer; (iii) a plasticizer; and (iv) an antisticking agent, and wherein the second pellet releases the bupropion in the lower gastrointestinal tract of a human patient [at a pH of about 7 (claims 53-55)].

It is respectfully submitted that the pending claims are patentable over the combination of Midha and Percel because a skilled artisan, reviewing the references, would not be led to the claimed three-component bupropion composition, tablet or capsule with the claimed enteric and sustained release coatings that exhibits the recited *in vivo* plasma profile with a reasonable expectation of success.

Midha teaches pulsatile delivery systems and states "a precise and effective pulsatile drug delivery system is difficult to formulate and manufacture". *See* Midha at p. 2, lines 3-4. While Midha provides an extensive list of membrane forming material that may be used to provide the pulsatile release of the active ingredient, Midha provides no motivation or suggestion to choose a pH dependent coating polymer selected from the group consisting of shellac, methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate and mixtures thereof for a first population of pellets and a water insoluble polymer combined with a methyl acrylic acid copolymer for a second population of pellets as presently claimed. Because of the large number of membrane coatings which Midha discloses, and the vast number of

combinations thereof, a skilled artisan would have no motivation to select the polymers of the claimed enteric and sustained release coatings, and accordingly, could not prepare a bupropion composition, tablet or capsule which exhibits the claimed *in vivo* plasma profile with a reasonable expectation of success.

In addition, Midha teaches away from the dosage forms of the presently amended claims wherein the drug is released in two pulses followed by a third continuous and gradual release of the drug. Midha teaches dosage forms in which the drug is to be released in either two or three pulses. Midha defines a pulsatile dosage form as one which "provides for an initial dose of drug followed by a release-free interval, after which a second dose of drug is released, followed by one or more additional release-free intervals and drug release 'pulses.'" Midha at p. 1, lines 21-25. In contrast, the compositions of the presently amended claims contain a sustained release component which continuously releases the drug over an interval rather than as a pulse followed by a release-free interval. Furthermore, as previously mentioned, Midha generally discloses the polymers utilized in the present claims, but provides no guidance to the skilled artisan to prepare a dosage form which has an immediate release component, a first pellet which contains a pH dependent polymer and a second pellet which contains a combination of a water insoluble polymer and a methyl acrylic acid copolymer to achieve a release of drug characterized by two pulses and a third gradual release. Accordingly, a skilled artisan would have no reasonable expectation of success of producing a dosage form which exhibits the release profile of the presently claimed composition to achieve the presently claimed *in vivo* plasma profile.

Moreover, because Midha teaches that the same coating material is used for both pellets and that pulsatile delivery is achieved by varying the thickness of the coating material (*see* Midha at p. 9, lines 5-17 and Examples 1 and 2), and because Midha only discloses bupropion as an

additional therapeutic agent that could be co-administered with methylphenidate (*see* Midha at p. 12, line 21-31 and p. 13, line 20), Midha fails to provide any guidance to the skilled artisan to select suitable polymer combinations, as presently claimed, to achieve a bupropion dosage form which exhibits the claimed *in vivo* plasma profile for once-a-day administration.

Percel teaches a pulsatile dosage form similar to Midha that employs two or more coated particles with different release rates. The different release rates are obtained by varying the coating weight and not the coating composition on the particles. *See* Percel at ¶ 19 and Examples 1, 2 and 4 (reporting different release profiles based upon coating weight). Applicants do not dispute that Percel teaches enteric coatings and sustained release coatings, however, both the enteric coating and the sustained release coating taught by Percel are applied to the same particle, not separate particles. In addition, Percel mentions bupropion as a potential drug, but fails to provide the skilled artisan with any guidance for selecting the amount of bupropion to be employed. Accordingly, Percel fails to provide any guidance to the skilled artisan to prepare a three-component system as presently claimed to achieve a bupropion dosage form which exhibits the claimed *in vivo* plasma profile for once-a-day administration.

Applicants respectfully submit that the combination of Midha and Percel would not lead a skilled artisan to the presently claimed invention. The combination of Midha and Percel would motivate a skilled artisan to prepare a multi-pellet dosage form wherein the same coating was applied to pellet cores but at varying coating weights to modify the release rate. The combined teachings of Midha and Percel would not suggest or motivate a skilled artisan to prepare a three-component system as recited in the pending claims wherein the drug release is controlled by separate and distinct pellets with separate and distinct coatings, i.e., an enteric coated pellet and a sustained release coated pellet, which were comprised of the presently claimed polymer

combinations. Moreover, the combined teachings of Midha and Percel fail to provide the skilled artisan with any guidance for selecting the amount of bupropion and ratio of coated bupropion pellets to obtain a once-a-day bupropion tablet or capsule that exhibits the *in vivo* plasma profile recited in the pending claims.

Because the combination of Midha and Percel fail to suggest a once-a-day bupropion tablet or capsule with an enteric coated pellet, wherein the coating comprises a pH dependent polymer selected from the group consisting of shellac, methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate and mixtures thereof, a plasticizer, and a lubricant, and a separate and distinct sustained release coated pellet, wherein the coating comprises a mixture of a water insoluble polymer and a methyl acrylic acid copolymer, a plasticizer, and an antisticking agent as required by the pending claims, Applicants submit that the pending claims are patentable over the combination of Midha and Percel.

In light of the foregoing amendments and remarks, Applicants respectfully submit that the claims of the present application are in proper form for allowance. Early and favorable consideration is therefore earnestly solicited and respectfully requested. If the Examiner does not believe the pending claims are in proper form for allowance, Applicants invite the Examiner to call the undersigned to discuss ways to further expedite prosecution of this application.

Respectfully submitted,

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